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PCT/SE 97/00566

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Applicant (s)

(21) *Patentansökningsnummer* *9601421-2*
Patent application number

(86) *Ingivningsdatum* *1996-04-12*
Date of filing

PRIORITY DOCUMENT

Stockholm, 1997-04-21

För Patent- och registreringsverket
For the Patent- and Registration Office

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NEW COMPOSITION

The field of the invention

The present invention is directed to a new pharmaceutical composition and its use in therapy, in particularly as an anaesthetic for use within the oral cavity.

Background and prior art

It is estimated that approximately 10-13 % of the population suffers from periodontal diseases with pathological periodontal pockets. In order to eliminate or control the disease and arrest further periodontal tissue destruction, periodontal pockets need repeated subgingival mechanical debridement/cleansing. The number of periodontal pockets in a patient may vary as can the pocket depth measurement. Approximately 40 % of all periodontal scaling procedures performed involve some kind of anaesthesia.

Ackumulation of bacterial plaque on teeth and in the gingival sulcus elicits an inflammatory response in the marginal gingiva which may spread in an apical direction and result in loss of tooth support with the formation of periodontal pockets. The object of mechanical debridement of periodontal pockets is to control and arrest further destruction of tooth support by removal of plaque and calculus from within the pockets.

The majority of the scaling procedures are performed by hygienists. The main use of anaesthesia techniques used in conjunction with periodontal scaling is either a nerve block or infiltration. Infiltration anaesthesia is either carried out alone or in combination with topical anaesthesia, mainly jelly, ointment or spray. However, the problem with existing topical products are lack of efficacy due to inadequate depth of penetration, too short duration and difficulties in administration due to spread, taste etc.

Thus, the problem underlying the present invention is to provide a pharmaceutical composition which would provide effective pain relief in conjunction with periodontal scaling and root planing following local administration. In other words, the object of the invention is to provide a local anaesthetic that can be applied in a facile manner in the oral cavity, and more precisely within periodontal pockets. A further object of the invention is to provide a pharmaceutical composition having a short onset time and an adequate duration for the intended procedure, with no inconvenient anaesthesia.

Outline of the invention

The problem identified above has now been solved by providing a new pharmaceutical composition comprising the following ingredients:

(i) One or more local anaesthetics in oil form in the formulation;

(ii) one or more surfactants;

(iii) optionally one or more taste masking agents;

(iv) water up to a total weight of the composition of 100 g .

The local anaesthetic in the final composition is one or more local anaesthetics in oil form as such, or a eutectic mixture formed by two or more local anaesthetics. The amount of the local anaesthetic in the oil phase depends on the pH-value of the formulation.

In a particularly preferred embodiment of the invention the local anaesthetic is a eutectic mixture of lidocaine base and prilocaine base.

The amount of the local anaesthetic or mixture of local anaesthetics is preferably in the range 0.5 - 20 % by weight, more preferably in the range 2-7 % by weight, based on the total weight of the composition.

By the wording "surfactant" we mean any agent that acts as an emulsifier and/or as a thickening agent. If more than one surfactant is present in the composition, at least one of the surfactants should have thermoreversible gelling properties. If only one surfactant is used in the composition, it must be selected with care and in suitable amounts so that it acts both as an emulsifier and as a thickening agent.

The surfactants are preferably selected from non-ionic surfactants, preferably from any non-ionic poloxamer known in the art.

Poloxamers are synthetic block copolymers of hydrophilic ethylene oxide chains and hydrophobic propylene oxide chains, having the general formula $HO-[C_2H_4O]_a-[C_3H_6O]_b-[C_2H_4O]_a-H$, a and b representing the number of the hydrophilic and hydrophobic chains respectively.

By choosing the surfactant or surfactants from surfactants having long hydrophobic chains and short hydrophobic chains in appropriate amounts, in combination with an appropriate amount of the local anaesthetic or mixture of local anaesthetics, it is possible to achieve a composition having suitable thermoreversible gelling properties, i.e. the system remains less viscous at room temperature, and upon application into a periodontal pocket the viscosity of the composition is increased. In other words, the pharmaceutical composition according to the present invention is less viscous at room temperature, i.e. below approximately 20 ° C. Above this temperature the composition is more viscous, providing the advantage of remaining in the periodontal pockets for the time necessary to induce local anaesthesia. The change in viscosity is reversible with temperature.

In a particularly preferred embodiment of the invention the surfactant is one or more of Lutrol F68®, which also has the name poloxamer 188 and wherein a= 79 and b=28, and Lutrol F127®, which also has the name poloxamer 407 and wherein a=101 and b=56, is used.

The total amount of surfactant(s) is preferably present in an amount of up to 50 % by weight, based on the total weight of the composition.

The pH-value of the pharmaceutical composition is adjusted with suitable acid or base in such a way that the final pH-value for the composition is:

(A) pH ≥ pK_a (local anaesthetic) - 1.0 if the composition comprises one local anaesthetic; or

(B) pH ≥ pK_a (local anaesthetic with the lowest pK_a value) - 1.0 if the composition comprises two or more local anaesthetics.

Since local anaesthetics by nature have an unpleasant bitter taste, one or more taste masking agents may be added to the pharmaceutical composition. The choice of taste masking agents will be appreciated by a person skilled in the art, but as an example any fruit flavours may be mentioned.

By topical application within the periodontal pocket, local anaesthesia is achieved in a very localised area of the pulp and soft tissue, without causing the often extensive soft tissues such as the tongue, cheek and lips, to get anaesthetized which is often the case with infiltration anaesthesia. Preferably the composition is applied into a periodontal pocket by means of a blunt needle, thereby facilitating the administration of the anaesthetic and giving an increased patient comfort.

The pharmaceutical composition of the present invention has a fast onset of action being from seconds and up to approximately 5 minutes.

The pharmaceutical composition according to the present invention is a microemulsion. This provides a maximal amount possible of the local anaesthetic in the oil phase, which in turn confers a fast onset of action. No external oil needs to be added to the composition. A further advantage is that a thermodynamically stable composition is achieved in a temperature range of 5-40 °C.

The pharmaceutical composition according to the present invention may advantageously also be used as a local anaesthetic on other mucous membranes than in the oral cavity. The composition is thus preferably used also vaginally, genitally and rectally.

The local anaesthetic(s) used for preparing a pharmaceutical composition according to the present invention may be selected from any local anaesthetic. Preferably the local anaesthetic is in a non-ionized form.

In the final composition the local anaesthetic or mixture of local anaesthetics are present in oil form.

The pharmaceutical composition according to the present invention is prepared by the following steps:

(i) the local anaesthetic(s) and the surfactant with the lowest molecular weight if more than one surfactants are used, are melted together;

(ii) a part of the water is slowly added to the melt (i) during homogenization, forming an emulsion concentrate;

(iii) if more than one surfactants are used, the surfactant with the higher molecular weight is dispersed in water;

(iv) the emulsion concentrate of step (ii) and part of the surfactant solution of step (iii) are thoroughly mixed;

(v) the pH-value is adjusted by the addition of a suitable acid or base;

(vi) the weight is adjusted with water to the final weight of the composition.

Detailed description of the invention

The invention will now be described in more detail by the following examples, which are not to be construed as limiting the invention.

Example 1

Lidocaine	2.50 g
prilocaine	2.50 g
Lutrol F68®	5.00 g
Lutrol F127®	16.25 g

purified water up to a total weight of the composition of 100 g

The composition was prepared by following the procedure described above, and the pH-value was adjusted by adding 2 M hydrochloric acid.

Example 2

Lidocaine	2.25 g
prilocaine	2.25 g
Lutrol F68®	3.5 g
Lutrol F127®	14.0 g

purified water up to a total weight of the composition of 100 g

The composition was prepared by following the procedure described above, and the pH-value was adjusted by adding 2 M hydrochloric acid.

Biological studies

A pharmaceutical composition according to the invention was applied to a human periodontal pocket with a blunt end needle. After an onset time of 20 - 45 seconds, a satisfactory anaesthetic effect had been achieved in order that periodontal scaling could be performed. The duration of the anaesthetic effect was 15-30 minutes.

Claims

1. A pharmaceutical composition comprising

(i) one or more local anaesthetics in oil form in the formulation;

(ii) one or more surfactants;

(iii) optionally one or more taste masking agents;

(iv) water up to a total weight of the composition of 100 g .

2. A pharmaceutical composition according to claim 1, wherein the amount of the local anaesthetic or mixture of local anaesthetics is present in an amount of 0.5 - 20 % by weight based on the total weight of the composition.

3. A pharmaceutical composition according to claim 1, wherein the active ingredient is a eutectic mixture of local anaesthetics, the total amount of local anaesthetics being present in an amount of 2-7 % by weight based on the total weight of the composition.

4. A pharmaceutical composition according to any of the preceding claims, wherein the active ingredient is a eutectic mixture of lidocaine and prilocaine.

5. A pharmaceutical composition according to claim 1, comprising more than one surfactant of which at least one is a surfactant having thermoreversible gelling properties.

6. A pharmaceutical composition according to any of the preceding claims, wherein the surfactant is a non-ionic surfactant.

7. A pharmaceutical composition according to claim 6, wherein the surfactant is a poloxamer.

8. A pharmaceutical composition according to claim 7, comprising the two surfactants Lutrol F68® and Lutrol F127®.

9. A pharmaceutical composition according to any of the preceding claims, the total amount of the surfactant(s) being present in an amount of up to 50 % by weight based on the total weight of the composition.

10. A pharmaceutical composition according to any of the preceding claims for use in therapy.

11. A pharmaceutical composition according to claim 10, the therapeutic indication being a local anaesthetic suitable for the oral cavity.

12. A pharmaceutical composition according to claim 11, the therapeutic indication being pain relief during periodontal scaling.

13. Use of a pharmaceutical composition according to claim 1, for the manufacture of a medicament for pain relief during periodontal scaling.

14. A method for the treatment of pain associated with periodontal scaling, whereby a pharmaceutical composition according to claim 1 is applied to a patient in the need of pain relief during periodontal scaling.

15. A process for the manufacture of a pharmaceutical composition according to claim 1, whereby

(i) the local anaesthetic(s) and the surfactant with the lowest molecular weight if more than one surfactants are used, are melted together;

(ii) a part of the water is slowly added to the melt (i) during homogenization, forming an emulsion concentrate;

(iii) if more than one surfactants are used, the surfactant with the higher molecular weight is dispersed in water;

(iv) the emulsion concentrate of step (ii) and part of the surfactant solution of step (iii) are thoroughly mixed;

(v) the pH-value is adjusted by the addition of a suitable acid or base;

(vi) the weight is adjusted with water to the final weight of the composition.

Abstract

The invention is directed to a novel pharmaceutical composition comprising one or more local anaesthetics in oil form, one or more surfactants, water and optionally a taste masking agent. The novel composition is advantageously used as a local anaesthetic for pain relief in the oral cavity.

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